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## **R E M A R K S**

### **The Restriction Requirement**

The Examiner has affirmed Applicants' election, without traverse, of the claims of Group I (2, 17, 35-39) and of species relating to heparan sulfate. All of the elected claims are deemed by the Examiner to read on the elected species.

### **Status of the Application**

Claims 35, 37, and 38 have been amended to correct several minor matters of form. The cross-reference to related cases in the specification has been updated.

Claims 2, 17, and 35-39 remain in the case.

### **The Rejections Under 35 U.S.C. § 102(b)**

Claims 2, 17, 35-39 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,956,347 issued on September 11, 1990 to Ban, *et al.* (hereinafter "Ban, *et al.*").

According to the Examiner, the claims are directed to a method of treating a condition, such as Alzheimer-type senile dementia or atherosclerosis, associated with toxicity caused by a peptide fragment of apolipoprotein E having a molecular weight of at least 5kD, by using an effective amount of heparan sulfate.

The Examiner alleges that Ban, *et al.* teach a treatment of Alzheimer-type senile dementia using a therapeutically effective amount of heparan sulfate like substance. In this regard, the Examiner directs Applicants' attention to Col. 4, lines 25-50. Ban, *et al.* further states that sulfomucopolysaccharide, a heparan sulfate like substance, is the conventional therapeutic modality

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for atherosclerosis (Col. 3, lines 1-10). Therefore, the Examiner argues that the heparan sulfate like substance of Ban, *et al.* includes heparan sulfate and any substance having a heparan sulfate moiety. Thus, the “critical elements” required by Applicants’ claims are taught by Ban, *et al.*

As to claims 2, 17, 35-37, the Examiner further alleges that the substances taught by Ban, *et al.* inherently possess the ability to prevent toxicity caused by the peptide fragment of apolipoprotein E recited in Applicants’ claims. Since this mechanism is considered to be an underlying mechanism for said treatment wherein it is naturally achieved when heparan sulfate is administered to the affected cell, the feature does not have patentable weight in this case and does not patentably distinguish over the prior art of record.

The rejection of claims 2, 17, and 35-37 is respectfully traversed.

Ban, *et al.* report the discovery that the administration of Ateroid, a drug used in the treatment of atherosclerosis, lipidic metabolism, and peripheral arteriopathies “alleviates the symptoms of Alzheimer-type senile dementia.” Ateroid comprises a mixture of sulfomucopolysaccharides that are obtained by extraction from animal tissues. Of course, Ateroid also contains a number of compounds other than sulfomucopolysaccharides. Of the sulfomucopolysaccharides, Ban, *et al.* teach that they are a mixture of heparin, heparan sulfate like substance, dermatan sulfate and chondroitin sulfate A and C. (Col. 4, line 9-27; *emphasis added*).

First, Ban, *et al.* nowhere teach or suggest that the “heparan sulfate like substance” is, in fact, heparan sulfate. It is respectfully submitted, that this “substance” is not heparan sulfate. An

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“analytical investigation,” of the type reported in Ban, *et al.* at Col. 4, lines 9-27, would have revealed the presence of heparan sulfate, or would have noted that the component is a mixture of heparan sulfate and/or heparan sulfate like substances. Contrary to the Examiner’s assertion, there is no teaching in Ban, *et al.* that the “heparan sulfate like substance” found as a component of Ateroid includes “heparan sulfate and any substance having a heparan sulfate moiety.” Nor is there any teaching that there is actually a therapeutically effective amount of heparan sulfate and any substance having a heparan sulfate moiety in the admixture known as Ateroid when administered at the suggested dosage.

Second, Ban, *et al.* notes the “uncertainties in the knowledge about the etiopathogenesis of ... Alzheimer type dementia, in particular ...” in the art at the time of the alleged Ban, *et al.* invention (See, Col. 2, lines 54-60). Ban, *et al.* does not teach or suggest a mechanism by which Ateroid would function to alleviate the symptoms of Alzheimer’s Disease, or even which, if any, components of the Ateroid mixture would be pharmacologically effective to treat or prevent Alzheimer’s Disease. Thus, without the forbidden application of hindsight, Ban, *et al.* can in no way teach a person of ordinary skill in the art how to practice reliably the invention taught by Applicant. This is true, even assuming *arguendo*, that the heparan sulfate like substance in the Ateroid mixture includes heparan sulfate as alleged by the Examiner.

In other words, Ban, *et al.* does not teach or suggest, to a person of ordinary skill in the art, that neural toxicity of fragments of apolipoprotein E having a molecular weight of at least 5kD can be prevented by administering a compound selected from the group consisting of polyvinyl

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sulfate, pentosan polysulfate, dextran sulfate, heparan sulfate and mixtures thereof as set forth in Applicants' independent claim 2. Nor does Ban, *et al.* teach or suggest that conditions associated with apolipoprotein E toxicity can be treated by the same method, as set forth in Applicants' independent claim 17, and hence the claims dependent thereon.

In conclusion, there is nothing in Ban, *et al.* that teaches or suggests that Alzheimer's Disease, or other disease conditions associated with apolipoprotein E toxicity, such as the conditions set forth in claims 38 and 39, can be prevented or treated by administration of heparan sulfate, or that apolipoprotein E, or large, physiological fragments of apolipoprotein E are toxic to cells, and that such toxicity can be mitigated by administration sulfomucopolysaccharides, and in particular heparan sulfate, or polyvinyl sulfate, pentosan polysulfate, dextran sulfate, and mixtures thereof as set forth in Applicants' independent claims 2 and 17.

In view of the foregoing, it is respectfully requested that the Examiner reconsider the present application, allow the claims, and pass the application for issue. If the Examiner believes that the prosecution of this case can be expedited by a telephone interview, the Examiner is requested to call attorney for Applicant at the telephone number indicated hereinbelow.

BJR:rk::ROA-01.AL3

Respectfully submitted,



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**Annexure 1 - Claims Rewritten to Show Amendments**

2.(Previously Amended) A method of preventing toxicity caused by a peptide fragment of apolipoprotein E having a molecular weight of at least 5kD to a cell comprising treating said cell with a compound wherein the compound is selected from the group consisting of polyvinyl sulfate, pentosan polysulfate, dextran sulfate, heparan sulfate and mixtures thereof.

17.(Previously Amended) A method of treating a mammal having a condition associated with toxicity caused by a peptide fragment of apolipoprotein E having a molecular weight of at least 5kD, comprising administering a composition comprising a pharmacologically effective amount of a compound, wherein the compound is selected from the group consisting of polyvinyl sulfate, pentosan polysulfate, dextran sulfate, heparan sulfate and mixtures thereof.

35.(Amended) The method of Claim 17, wherein inhibiting treating a mammal having a condition associated with toxicity caused by a peptide fragment of apolipoprotein E toxicity comprises inhibiting binding of apolipoprotein E or fragments of apolipoprotein E to a cell.

36.(Original) The method of Claim 35, wherein the fragments of apolipoprotein E comprises residues 141-147 of apolipoprotein E.

37.(Amended) The method of Claim 17, wherein inhibiting treating a mammal having a condition associated with toxicity caused by a peptide fragment of apolipoprotein E toxicity comprises inhibiting production of a peptide fragment of apolipoprotein E comprising residues 141-147 of apolipoprotein E.

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38.(Amended) The method of Claim 17, wherein the condition is selected from the group consisting of Alzheimer's-type senile dementia, a condition associated with cerebral amyloidosis and ~~hyperlipidemia~~ hyperlipidemia.

39.(Original) The method of Claim 17, wherein the condition is selected from the group consisting of coronary heart disease, atherosclerosis, head injury, ischemic stroke, intracerebral hemorrhage, normal pressure hydrocephalus, HIV-associated dementia and HIV-associated peripheral neuropathy.

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**Annexure 2 - Text of Specification Rewritten to Show Amendments**

Please amend the paragraph on page 1, lines 5-8, under the heading "Related Applications" as follows:

This is a continuation of U.S. Serial No. 09/255,331 filed on February 22, 1999, now U.S. Patent No. 6,277,874 issued on August 21, 2001, U.S. Serial No. 09/255,331 is a continuation-in-part of U.S. Serial No. 09/214,742, filed January 6, 1999, now U.S. Patent No. 6,245,751 issued on June 12, 2001, which claims priority from international application PCT/US97/11836, filed July 8, 1997, which ~~is a continuation-in-part~~ claims the benefit of U.S. Serial No. 60/021,405, filed July 9, 1996, all hereby expressly incorporated by reference.